1,168,430

# PATENT SPECIFICATION

NO DRAWINGS

1,168,430

Date of Application (No. 4748/69) and filing Complete Specification: 28 Jan., 1969.

Application made in United States of America (No. 719,272) on 5 April, 1968.

Complete Specification Published: 22 Oct., 1969.

Index at acceptance:—C2 C(215, 22Y, 220, 25Y, 250, 252, 253, 28X, 30Y, 32Y, 322, 332, 36Y, 365, 660, 670, 671, 79Y, 790, 175—193—286, 176—270—277, LW)

International Classification:—C 07 d 99/04

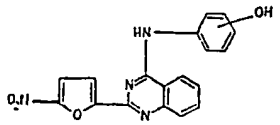
COMPLETE SPECIFICATION

## Improvements in or relating to Nitrofuryl Quinazolines

We, THE NORWICH PHARMACAL COMPANY, a corporation organized and existing under the laws of the State of New York, United States of America of 17 Eaton Avenue, Norwich, New York 13815, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 4-substituted-nitrofuryl quinazolines and to a process for the preparation thereof. The invention is also concerned with pharmaceutical compositions containing the said compounds.

More particularly, the present invention provides 4 - (hydroxyanilino) - 2 - (5 - nitro-2 - furyl)quinazolines of the formula:




The compounds of the above formula possess a very high order of anti-bacterial activity particularly in respect to those organisms prevalent in the veterinary field.

It is known from United Kingdom Patent Specification No. 1,101,179 that certain 4-substituted - 2 - (5 - nitro - 2 - furyl)quinazolines are anti-bacterial agents having a broad anti-bacterial spectrum and that the compounds having a 4-amino substituent also possess activity in supressing *in vivo* lethal infections provoked by *Staphylococcus aureus* in animals.

Surprisingly the compounds of this invention do not possess such *in vivo* activity. They do, however, possess an unexpectedly greater *in vitro* anti - bacterial potency particularly toward those organisms such as *Streptococcus agalactiae* and *Staphylococcus aureus*, commonly occurring pathogens in bovine mastitis; *Salmonella typhimurium* and *Escherichia coli*, organisms of concern in calf enteritis; *Pasturella, multocida*, a causative agent in fowl cholera; and *Moraxella bovis*, frequently associated with infectious keratoconjunctivitis in cattle.

The following table is representative of the anti-bacterial effect of the ortho-, meta-, and parahydroxyanilino - 2(5 - nitro - 2 - furyl)-quinazolines of this invention:

| Compound | Minimum inhibitory conc. in mcg./ml. | | | | | |
|---|---|---|---|---|---|---|
| | *S. agalactiae* | *S. aureus* | *S. typhimurium* | *E. coli* | *P. multocida* | *M. bovis* |
| ortho- | 1.0 | 0.03 | 0.5 | 0.5 | 1.0 | — |
| meta- | 0.06 | 0.03 | 1.0 | 1.0 | 0.06 | 0.003 |
| para- | 0.015 | 0.06 | 0.5 | 1.0 | 0.06 | 0.003 |

The compounds of this invention are adapted to be admixed with excipients which are common to the pharmaceutical art to provide pharmaceutical compositions in various forms, such as ointments, dusts, suspensions and gels, suitable for application to control and eradicate bacterial invaders. The amount of a compound of this invention to be incorporated in

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such compositions ranges from 0.1 to 1.0 percent by weight thereof, such concentration being sufficient to achieve the effect desired.

The compounds of this invention are readily prepared. The process which is currently preferred comprises reacting a 4 - halo - 2 - (5 - nitro - 2 - furyl)quinazoline with ortho-, meta- or para-hydroxyaniline. The reaction is preferably conducted in the presence of a solvent inert to the reactants and preferably under the influence of heat to hasten the reaction. The 4 - halo - 2 - (5 - nitro - 2 - furyl)-quinazolines which are used as starting materials are claimed in Patent Specification No. 1,101,180.

The following Examples are given to illustrate the manner in which the invention may be carried into effect.

EXAMPLE I

4-(*o*-Hydroxyanilino)-2-(5-nitro-2-furyl)quinazoline

A 1 litre three-neck flask, fitted with a stirrer, was charged with 35 g. (0.127 mole) of 4 - chloro - 2 - (5 - nitro - 2 - furyl)-quinazoline and 28.5 g. (0.26 mole) of *o*-hydroxyaniline in 500 ml. of dimethylformamide. The solution was heated on a steam bath for two hours. The solution was diluted with water until a solid began to separate. The mixture was cooled. The crude product was collected by filtration, and recrystallized from dilute aqueous dimethylformamide. The product separated as orange platelets melting at 275° C. dec. (corr.) in a yield of 35 g. (70.5%).

Anal. Calcd. for $C_{18}H_{12}N_4O_4$: C, 62.07; H, 3.47; N, 16.09.
Found: C, 61.89; H, 3.57; N, 15.90.

EXAMPLE II

4-(*m*-Hydroxyanilino)-2-(5-nitro-2-furyl)quinazoline

A 1 litre three-neck flask, fitted with a stirrer, was charged with 35 g. (0.127 mole) of 4 - chloro - 2 - (5 - nitro - 2 - furyl) quinazoline and 28.5 g. (0.26 mole) of *m*-hydroxyaniline in 500 ml. of dimethylformamide. The solution was heated on a steam bath, with stirring, for 2 hours. The solution was diluted with water until a solid began to separate. The mixture was cooled; the crude product was collected by filtration, and recrystallized from dilute aqueous dimethylformamide. The product separated as yellow needles melting at 284° C. dec. (corr.) in a yield of 39 g. (88%).

Anal. Calcd. for $C_{18}H_{12}N_4O_4$: C, 62.07; H, 3.47; N, 16.09
Found: C, 62.05; H, 3.54; N, 16.10

EXAMPLE III

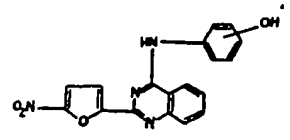
4-(*p*-Hydroxyanilino)-2-(5-nitro-2-furyl)quinazoline

A solution of 30.2 g (0.11 mole) of 4-chloro-2 - (5 - nitro - 2 - furyl)quinazoline and 27.2 g. (0.25 mole) of *p* - hydroxyaniline in 500 ml. of dimethylformamide was heated on a steam bath for two hours. The solution was diluted with water until a dark solid had separated. The mixture was cooled. The solid was collected by filtration and recrystallized from dilute aqueous dimethylformamide. The product, melting at 286° to 288° C. dec. (corr.), was collected by filtration in a yield of 35 g. (91.5%).

Anal. Calcd. for $C_{18}H_{12}N_4O_4$: C, 62.07; H, 3.47; N, 16.09
Found: C, 62.01; H, 3.58; N, 15.78

WHAT WE CLAIM IS:—

1. A 4 - (hydroxyanilino) - 2 - (5 - nitro-2 - furyl)quinazoline of the formula:

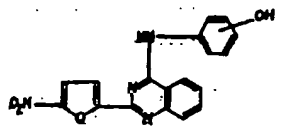


2. 4 - (*o*-Hydroxyanilino) - 2 - (5 - nitro-2 - furyl) quinazoline.

3. 4 - (*m*-Hydroxyanilino) - 2 - (5 - nitro-2 - furyl) quinazoline.

4. 4 - (*p*-Hydroxyanilino) - 2 - (5 - nitro-2 - furyl) quinazoline.

5. A process for the preparation of a compound of the formula:



which comprises reacting a 4 - halo - 2 - (5 -

nitro - 2 - furyl)quinazoline with ortho-, meta- or para-hydroxyaniline.

6. A process according to claim 5, in which the reaction is conducted in the presence of a solvent inert to the reactants and under the influence of heat.

7. A process according to claim 6 in which the solvent is dimethylformamide.

8. A process for the preparation of a 4 - (hydroxyanilino) - 2 - (5 - nitro - 2 - furyl)quinazoline substantially as hereinbefore described with reference to the Examples.

9. A pharmaceutical composition comprising a 4 - (hydroxyanilino) - 2 - (5 - nitro-2 - furyl)quinazoline in admixture with a pharmacologically acceptable excipient.

10. A composition according to claim 9, in which the quinazoline compound is present in an amount of 0.1 to 1.0 percent by weight of the total composition.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.